Cardiovascular Diabetology

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# Association of baseline and trajectory of triglyceride-glucose index with the incidence of cardiovascular autonomic neuropathy in type 2 diabetes mellitus

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## Abstract

**Background** Cardiovascular autonomic neuropathy (CAN), characterized by disrupted autonomic regulation of the cardiovascular system, is a frequent complication associated with diabetes. The triglyceride-glucose (TyG) index represents a precise insulin resistance indicator. However, the influence of baseline and prolonged TyG index patterns on CAN risk in type 2 diabetes remains unclear.

**Methods** Based on the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, multivariate logistic regression models and restricted cubic splines (RCS) were deployed for elucidating the relation between baseline TyG index and the incidence of CAN. The area under the curve (AUC) of receiver operating characteristic (ROC) curve was used to assess the diagnostic value of the TyG index in predicting the risk of CAN. The relationship between TyG trajectory and the occurrence of CAN in individuals with diabetes was examined using Kaplan-Meier curve and a multivariable Cox proportional hazards regression model. Subgroup analysis was used to assess the robustness of the results. Additionally, we explored the impact of intensive glycemia treatment on the relationship between trajectory of TyG index and CAN risk.

**Results** In this study, these in the top quartile of the TyG index had a greater likelihood of developing CAN (TyG index Q4 vs. Q1 in Model II, OR = 1.29, 95% CI 1.03–1.62, $P = 0.027$). RCS indicated a rising trend in the TyG index in relation to the incidence of CAN. The AUC of the TyG index for predicting the occurrence of CAN was 0.636 (95% CI 0.620–0.651; $P < 0.001$), with the cut-off value of 0.208. During a 7-year follow-up period, three unique TyG trajectories were recognized: class 1 ($n = 431$, 23.26%), class 2 ($n = 798$, 27.57%), and class 3 ($n = 293$, 31.71%). Notable discrepancies in CAN risk across various trajectories were identified in Kaplan-Meier curve ($P < 0.001$). Cox regression analysis indicated that individuals in class 3 experienced a greater incidence of CAN in comparison to those in class 1 after adjusting for all covariates. Subgroup analysis found no significant effect modification in this relationship. Additionally, in the

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intensive glycemia group, class 2 had a reduced risk of CAN, while class 3 had an increased risk when compared to standard glycemia group.

**Conclusion** Increased baseline levels and long-term trajectory of TyG index are associated with an increased incidence of CAN. Intensive glycemic therapy might influence the association between the trajectory of TyG index and the chance of developing CAN.

**Keywords** Triglyceride-glucose index, Trajectory, Diabetes, Cardiovascular autonomic neuropathy

## Introduction

Cardiac autonomic neuropathy (CAN) refers to the dysfunction of the autonomic nerve fibers that regulate cardiac function and vascular systems [1]. CAN presents with resting tachycardia or orthostatic hypotension, which can be identified through abnormal heart rate variability (HRV) [2]. Due to its late-onset symptoms, CAN is often misdiagnosed. CAN affects up to 34% of individuals with diabetes and acts as a standalone indicator of serious outcomes such as cardiovascular disease (CVD), heart failure, and cardiac death [3]. Several factors such as uncontrolled blood glucose, prolonged diabetes, hypertension, and smoking contribute to the onset and progression of CAN [4]. Despite stringent control of these factors, the risk of CAN remains high. Therefore, it is needed to explore unidentified elements associated with CAN.

Insulin resistance, marked by diminished tissue response to insulin, significantly contributes to the onset of atherosclerotic cardiovascular disease [5]. The triglyceride-glucose (TyG) index is a dependable marker of insulin resistance and is implicated in obesity, nonalcoholic fatty liver disease, hypertension and atherosclerosis [6–9]. Furthermore, Ziegler et al. has shown that insulin resistance contributes to the onset of CAN in individuals with diabetes [5]. Nonetheless, the utility of the TyG index in predicting CAN is still not well established. In addition, most studies have only assessed TyG index at a single point in time, leaving its long-term impact on CAN risk unexplored [10].

Trajectory of TyG index identifies TyG patterns in timing, direction, and magnitude of change [11]. This approach addresses the limitations of relying on a single measurement, which may overlook developmental differences, thereby providing a comprehensive understanding of the entire progression. Blood glucose control is a crucial aspect of diabetes management to prevent complications such as cardiovascular and renal diseases [12]. This study aimed to explore how TyG index and its trajectory relate to the incidence of CAN from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, and the importance of glycemic therapy strategies in influencing the link between trajectory of TyG index and CAN risk.

## Methods

### Study design

The ACCORD trial, a multicenter randomized trial in the U.S. and Canada, aims to determine if intensive glycemia treatment reduces severe cardiovascular outcomes and mortality in type 2 diabetes (T2D) patients [13–18]. Participants wrote informed consent for their involvement in the ACCORD study (ClinicalTrials.gov number, NCT00000620). In this study, we extracted 10,251 patients with T2D from the ACCORD trial. To investigate the potential link between baseline TyG index and CAN occurrence, 2,311 participants were excluded from the present analysis: 55 had missing TyG baseline data; 2096 had missing CAN baseline data; and 160 were missing covariate data. To further examine how fluctuations in the TyG index over time relate to the risk of CAN, 2,269 participants were removed: those who had a CAN diagnosis at baseline ($n = 1,588$), lacked CAN data during follow-up ($n = 650$), or had fewer than three valid TyG index measurements before CAN diagnosis ($n = 31$).

### TyG index calculation

According to the ACCORD protocol, lipid levels were either measured at a local lab or sourced from medical records [19]. If medical records didn't have lipid levels from the past 12 months, a blood test was required at the local lab. The TyG index, a metric derived from triglyceride (TG) and fasting blood glucose (FBG) levels, was assessed using the formula TyG index = ln [TG [mg/ dL]× FBG [mg/dL] /2] [20–23].

### Cardiac autonomic neuropathy

CAN was evaluated using HRV measures obtained from a digital 12-lead ECG. Baseline standard ECG recordings were performed over 10 consecutive seconds using the GE MAC 1200 electrocardiograph system (GE, Milwaukee, WI) with participants resting supine following an overnight fast. ECG signals were acquired at a speed of 25 mm/s and a calibration of 10 mm/mV. After acquisition, the ECG recordings were electronically transmitted to a centralized reading center for quality review and processing using standardized procedures. Signal processing included filtering, sampling, and the management of ectopic beats. HRV indices were derived from the digitalized ECGs, including the standard deviation of

all normal-to-normal R-R intervals (SDNN) and the root mean square of successive differences between normal-to-normal R-R intervals (rMSSD). CAN was determined if both SDNN (< 8.2 ms) and rMSSD (< 8.0 ms) fell below established cutoffs according to previous studies [1, 24].

### Covariates

Covariates were selected a priori based on their established or potential associations with TyG and CAN. These included demographic factors (age, gender, race, ethnicity, and education), anthropometric measurements (body mass index [BMI]), clinical indicators (systolic and diastolic blood pressure [SBP and DBP], QT index, glycated hemoglobin [HbA1c], fasting plasma glucose [FPG], triglycerides, total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and alanine transaminase [ALT]), kidney function markers (serum creatinine and estimated glomerular filtration rate [eGFR], calculated using the CKD-EPI equation), and lifestyle factors (smoking and alcohol status). Additionally, medical history (duration of CVD, hypertension, stroke, and diabetes) and medication use (including angiotension converting enzyme inhibitors/angiotensin II receptor blockage [ACEI/ARB], beta-blockers, calcium channel blockers [CCB], diuretics, statins, fibrates, cholesterol absorption inhibitors, biguanides, meglitinides, sulfonylureas, thiazolidinediones, insulin and glycemic therapies) were included as covariates. Data for these variables were obtained from the ACCORD study following standardized protocols. Lipid levels and HbA1c were measured at a central laboratory using enzymatic or high-performance liquid chromatography (HPLC) methods, and blood pressure was assessed as the average of three seated measurements using an automated device [25–28].

### Statistical analysis

Normally distributed continuous variables were presented as mean ± standard deviation and were analyzed using the t-test. Non-normally distributed continuous variables were presented as the median (interquartile range, IQR), and were analyzed using the Kruskal Wallis H test. Categorical variables were presented as absolute values (n) or percentages (%) and were analyzed using the chi-square test. The TyG index has been classified into four groups: Q1 group (< 9.016), Q2 group (9.016–9.479), Q3 group (9.479–9.957), and Q4 group (≥ 9.957). Three multivariate logistic regression models assessed the relationship between the TyG index and CAN prevalence in the study. The crude model included no adjustments. Model I controlled for age, gender, ethnicity, and BMI. While Model II accounted for all covariates. The relationship between exposure and outcome was examined through restricted cubic splines (RCS). The predictive efficacy of the TyG index for patients with CAN was evaluated using the area under the curve (AUC) and 95% confidence interval (CI) of the receiver operating characteristic (ROC) curve based on the fully adjusted model [29–31]. Subgroup analyses were performed to further prove the stability of the model. We applied a latent growth curve model (LGCM) to identify subgroups with similar trajectory of TyG index over follow-up time. We identified the ideal number of classes using assignment probabilities (> 70%), the lowest Bayesian Information Criterion (BIC), and class sizes (> 5%). Three optimal TyG index trajectories were identified as class 1, class 2, and class 3. Kaplan-Meier curve and Cox proportional hazards model were used to analyze the relationship of TyG index trajectory with CAN incidence. Finally, we examined the association between TyG index trajectory groups and CAN risk according to different glycaemic therapy subgroups were also explored using cox proportional hazards regression model. Data analyses were performed with R (v4.3.3) and the lcmm toolkit (v1.9.5), considering two-sided $P < 0.05$ as statistically significant.

## Results

### Characteristics stratified by baseline TyG index

Baseline characteristics of the total population and groups stratified by with or without CAN were presented in Table 1. A total of 7940 participants were included in this study and CAN was present in 20.0% of participants ($n = 1588$). Patients with CAN had higher BMI, QT index, HbA1c, FPG, triglycerides, and TyG index, along with lower LDL, HDL, eGFR and use beta blocker compared to those without CAN. Moreover, they were more likely to be male and White, smoke, and have longer duration of diabetes and insulin. No significant differences were observed in age, education, SBP, DBP, total cholesterol, ALT, CVD history, hypertension, stroke, use of ACEI/ARB, CCB, diuretics, statin, fibrates, cholesterol absorption inhibitors, biguanides, meglitinides, sulfonylurea, thiazolidinediones, and glycemic therapy.

### Association of baseline TyG index with incidence of CAN

The association of the TyG index with CAN risk is shown in Table 2. Multivariate logistic regression revealed that both continuous and categorical TyG index values were linked to a higher risk of CAN. After accounting for confounding variables, the highest TyG index quartile remained linked to an increased risk of CAN (Q4 vs. Q1, OR = 1.29, 95% CI: 1.03–1.62, $P = 0.027$, Model II). The RCS indicated a rising trend in CAN risk with TyG index levels ($P$ for nonlinearity = 0.378, $P$ for overall = 0.03) (Fig. 2). As shown in Supplementary file 1: Fig. 1, The AUC of CAN evaluated by TyG index was 0.636 (95% CI 0.620–0.651; $P < 0.001$). The cut-off value of TyG index to predict the incidence of CAN was 0.208, the sensitivity

**Table 1** Baseline characteristics of participants

| Variables | Total (*n* = 7940) | Non-CAN (*n* = 6352) | CAN (*n* = 1588) | *P*-value |
|---|---|---|---|---|
| Age, (years) | 61.7 (57.6, 66.6) | 61.7 (57.5, 66.6) | 61.8 (57.8, 66.6) | 0.486 |
| Gender, n (%) | | | | < 0.001 |
| Female | 3162 (39.82) | 2617 (41.2) | 545 (34.32) | |
| Male | 4778 (60.18) | 3735 (58.8) | 1043 (65.68) | |
| Ethnicity, n (%) | | | | < 0.001 |
| White | 4978 (62.7) | 3907 (61.51) | 1071 (67.44) | |
| Non-White | 2962 (37.3) | 2445 (38.49) | 517 (32.56) | |
| BMI, ($kg/m^2$) | 31.81 (28.2, 35.84) | 31.7 (28.15, 35.68) | 32.09 (28.44, 36.57) | 0.003 |
| Education, n (%) | | | | 0.957 |
| Less than high school graduate | 1122 (14.13) | 900 (14.17) | 222 (13.98) | |
| High school grad or GED | 2117 (26.66) | 1693 (26.65) | 424 (26.7) | |
| Some college or technical school | 2624 (33.05) | 2091 (32.92) | 533 (33.56) | |
| College graduate or more | 2077 (26.16) | 1668 (26.26) | 409 (25.76) | |
| SBP, (mmHg) | 135 (124, 147) | 135 (125, 147) | 135 (124, 146) | 0.286 |
| DBP, (mmHg) | 75 (68, 82) | 75 (68, 82) | 75 (68, 82) | 0.550 |
| QT Index | 100.96 (98.34, 104.32) | 100.9 (98.34, 104.23) | 101.14 (98.21, 104.91) | 0.022 |
| HbA1c, (%) | 8.1 (7.6, 8.8) | 8.1 (7.5, 8.8) | 8.25 (7.7, 9.1) | < 0.001 |
| FPG, (mg/dL) | 168 (139, 204) | 166 (138, 201) | 176 (144, 215) | < 0.001 |
| Triglycerides, (mg/dL) | 156 (107, 230) | 154 (106, 227) | 165 (113, 245.25) | < 0.001 |
| Total cholesterol, (mg/dL) | 179 (154, 207) | 178 (155, 207) | 179 (153, 206) | 0.794 |
| LDL, (mg/dL) | 101 (81, 125) | 101 (82, 125) | 99 (80, 123) | 0.029 |
| HDL, (mg/dL) | 40 (34, 48) | 40 (34, 48) | 39 (33, 47) | 0.011 |
| ALT, (mg/dL) | 24 (18, 33) | 24 (18, 33) | 24 (18, 32) | 0.839 |
| eGFR, ($mL/min/1.73m^2$) | 89.9 (76.2, 105.4) | 90.1 (76.4, 105.8) | 89.2 (73.5, 103.9) | 0.006 |
| Smoking status, n (%) | | | | 0.031 |
| Never | 3365 (42.38) | 2728 (42.95) | 637 (40.11) | |
| Former | 3475 (43.77) | 2772 (43.64) | 703 (44.27) | |
| Current | 1100 (13.85) | 852 (13.41) | 248 (15.62) | |
| Alcohol status, n (%) | 1881 (23.69) | 1539 (24.23) | 342 (21.54) | 0.026 |
| CVD history, n (%) | 2727 (34.35) | 2153 (33.89) | 574 (36.15) | 0.097 |
| Hypertension, n (%) | 5990 (75.44) | 4783 (75.3) | 1207 (76.01) | 0.580 |
| Stroke, n (%) | 457 (5.76) | 359 (5.65) | 98 (6.17) | 0.462 |
| DM duration, (years) | 9 (5, 15) | 9 (5, 15) | 10 (6, 16.25) | < 0.001 |
| ACEI/ARB, n (%) | 5490 (69.14) | 4380 (68.95) | 1110 (69.9) | 0.485 |
| Beta blocker, n (%) | 2323 (29.26) | 1913 (30.12) | 410 (25.82) | < 0.001 |
| CCB, n (%) | 1497 (18.85) | 1197 (18.84) | 300 (18.89) | 0.994 |
| Diuretics, n (%) | 2857 (35.98) | 2259 (35.56) | 598 (37.66) | 0.127 |
| Statin, n (%) | 5063 (63.77) | 4068 (64.04) | 995 (62.66) | 0.318 |
| Fibrates, n (%) | 461 (5.81) | 373 (5.87) | 88 (5.54) | 0.657 |
| Cholesterol absorption inhibitors, n (%) | 176 (2.22) | 150 (2.36) | 26 (1.64) | 0.097 |
| Biguanides, n (%) | 5165 (65.05) | 4153 (65.38) | 1012 (63.73) | 0.228 |
| Meglitinides, n (%) | 200 (2.52) | 169 (2.66) | 31 (1.95) | 0.128 |
| Sulfonylurea, n (%) | 4287 (53.99) | 3424 (53.9) | 863 (54.35) | 0.774 |
| Thiazolidinediones, n (%) | 1769 (22.28) | 1402 (22.07) | 367 (23.11) | 0.392 |
| Insulin, n (%) | 848 (10.68) | 611 (9.62) | 237 (14.92) | < 0.001 |
| Glycemic therapy, n (%) | | | | 0.337 |
| Standard glycemia | 3988 (50.23) | 3208 (50.5) | 780 (49.12) | |
| Intensive glycemia | 3952 (49.77) | 3144 (49.5) | 808 (50.88) | |
| TyG index | 9.48 (9.02, 9.96) | 9.45 (9, 9.94) | 9.58 (9.1, 10.05) | < 0.001 |

CAN, cardiovascular autonomic neuropathy; BMI, body mass index; GED, general educational development; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; LDL, low density lipoprotein; HDL, high density lipoprotein; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; ACEI/ARB, angiotension converting enzyme inhibitors/angiotensin II receptor blockage; CCB, calcium channel blockers; TyG, triglyceride-glucose

**Table 2** Association of TyG index at baseline with the incident of CAN

| | Crude Model | | Model I | | Model II | |
|---|---|---|---|---|---|---|
| | **Crude OR (95%CI)** | ***P*-value** | **Adjusted OR (95%CI)** | **P-value** | **Adjusted OR (95%CI)** | ***P*-value** |
| TyG index | 1.25 (1.16, 1.35) | < 0.001 | 1.21 (1.12, 1.31) | < 0.001 | 1.19 (1.04, 1.38) | 0.013 |
| Q1 | Reference | | Reference | | Reference | |
| Q2 | 1.03 (0.87, 1.21) | 0.740 | 0.99 (0.84, 1.17) | 0.936 | 1.03 (0.87, 1.23) | 0.724 |
| Q3 | 1.23 (1.05, 1.44) | 0.011 | 1.16 (0.99, 1.37) | 0.068 | 1.17 (0.98, 1.41) | 0.083 |
| Q4 | 1.47 (1.26, 1.72) | < 0.001 | 1.39 (1.18, 1.63) | < 0.001 | 1.29 (1.03, 1.62) | 0.027 |
| *P* for trend | < 0.001 | | < 0.001 | | 0.016 | |

The crude model did not adjust for any covariates. Model I adjusted for age, gender, ethnicity and BMI. Model II adjusted for all covariates. TyG, triglyceride-glucose; CAN, cardiovascular autonomic neuropathy; OR, odd ratio; CI, confidence interval; BMI, body mass index

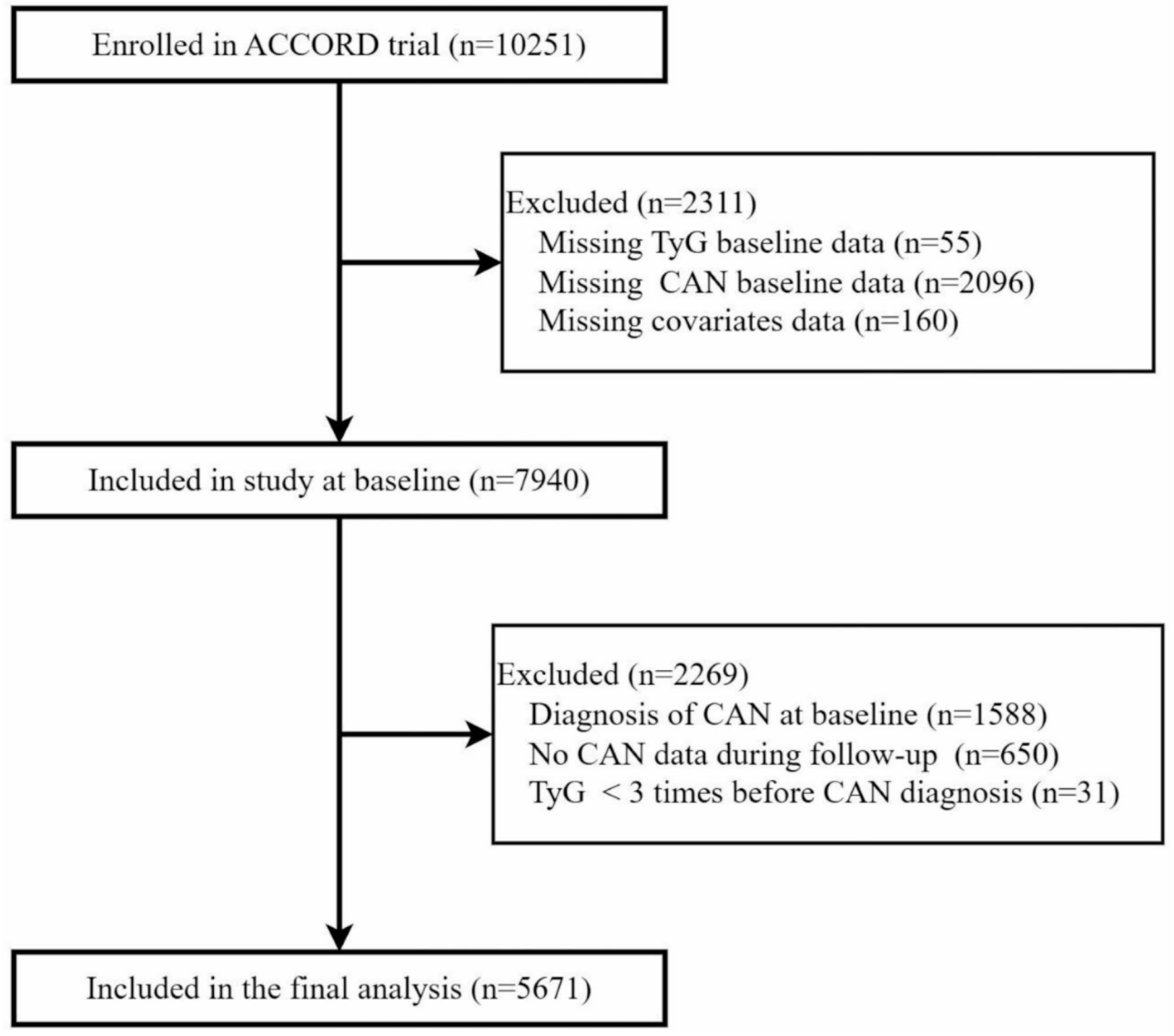


**Fig. 1** Flowchart of participants included in this study. ACCORD, Action to Control Cardiovascular Risk in Diabetes; TyG, triglyceride-glucose; CAN, cardiovascular autonomic neuropathy

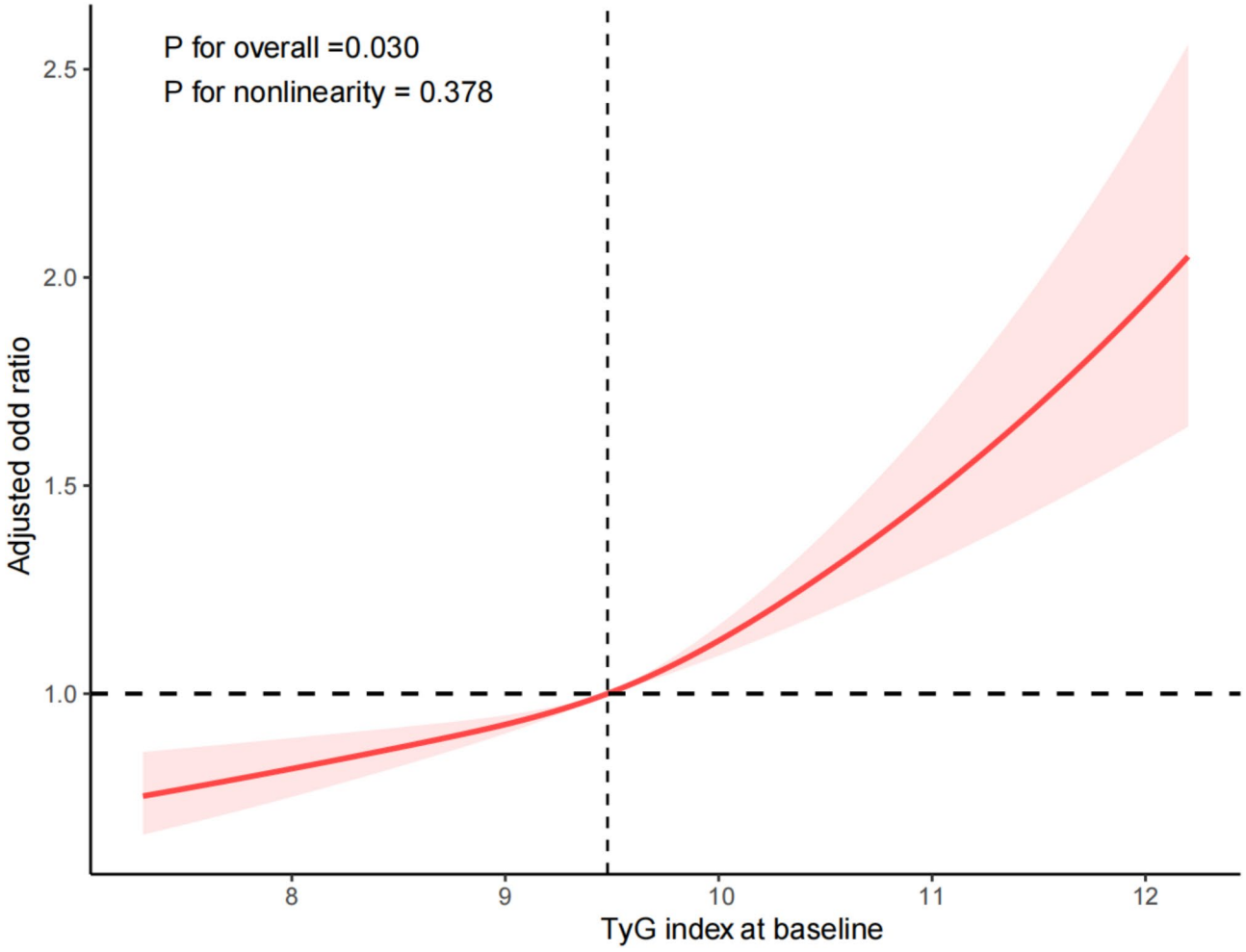


**Fig. 2** Association of TyG index at baseline with the incidence of CAN using RCS curve. The RCS curve adjusted for all covariates. TyG, triglyceride-glucose; CAN, cardiovascular autonomic neuropathy; RCS, restricted cubic spline

was 0.563, and the specificity was 0.636. Subgroup analysis revealed no significant interactions with age, gender, ethnicity, BMI, education, SBP, DBP, HbA1c, total cholesterol, LDL, HDL, eGFR, smoking status, alcohol status, hypertension, and glycemia therapy (all $P > 0.05$) in Supplementary file 2: Table 1.

#### Features categorized by trajectory of TyG index

The optimal trajectory categories were identified using minimum BIC and maximum entropy, resulting in three distinct groups, detailed in Supplementary file 2: Table 2. The trajectory trend was categorized into class 1, class 2 and class 3 group as presented in Fig. 3. As shown in Supplementary file 2: Table 3, individuals in class 1 had lower TyG index and incidence of outcomes than those in class 2 and class 3 group. Supplementary file 2: Table 4 displayed the demographic and clinical characteristics across different TyG index trajectories. Statistical differences among trajectory groups were observed for all variables except QT index, alcohol status, hypertension, stroke, ACEI/ARB use, diuretics, statins, meglitinides, sulfonylureas, thiazolidinediones, and insulin.

#### Association between the trajectory of TyG index and CAN risk

Kaplan-Meier curve illustrated varying CAN incidences across the three trajectories as shown in Fig. 4. Long-term outcomes revealed significant differences between groups, with class 3 showing a higher CAN incidence (log-rank test $P < 0.001$). The association of the trajectory of TyG index with CAN risk is presented in Table 3. Cox regression revealed that class 3 had a 1.52-fold higher CAN risk compared to class 1 (OR = 1.52, 95% CI: 1.26–1.83, $P < 0.001$) . Supplementary file 2: Table 7 showed no significant interactions between TyG trajectories and CAN incidence in age, gender, ethnicity, BMI, education, SBP, DBP, HbA1c, total cholesterol, LDL, HDL, eGFR, smoking status, alcohol status, and hypertension ($P > 0.05$).

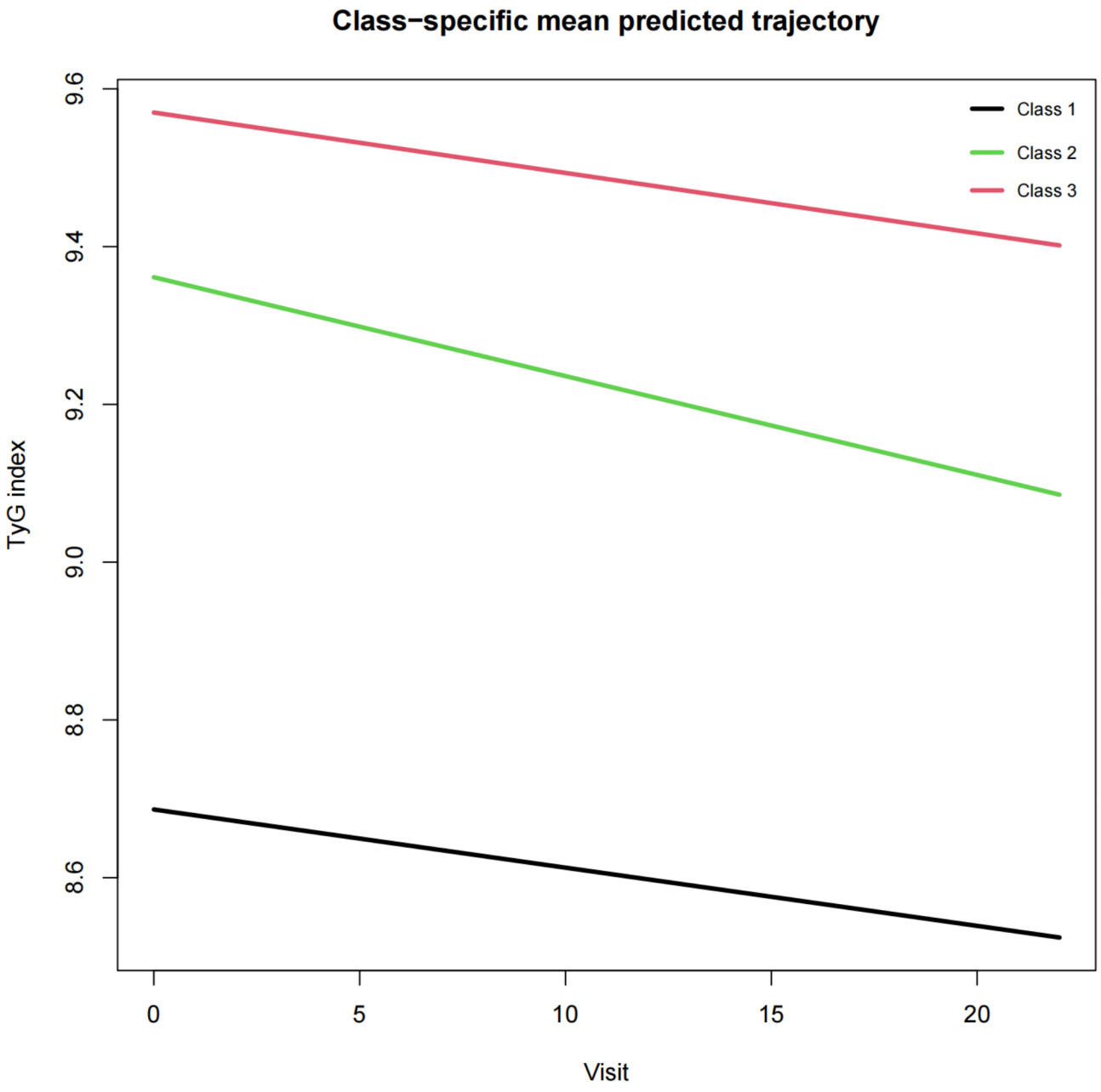


**Fig. 3** The trajectories of TyG index by follow-up time. TyG, triglyceride-glucose

**Glycemic therapy in the association between the trajectory of TyG index and CAN incidence**

As shown in Supplementary file 2: Table 5, in standard glycemia group, participants in class 2 and class 3 had a significantly higher risk of CAN compared to the reference group in the crude model. Similar patterns were also observed in model I and model II for the standard glycemia group. In intensive glycemia group, the risk was significantly higher for class 3 in crude, model I and model II, respectively. Moreover, we found that glycaemic therapy interacted with the association between trajectory of TyG index and CAN incidence. As shown in Supplementary file 2: Table 6, compared to standard glycemia group, the risk of CAN in intensive glycemic group was not significantly different in the class 1. In the intensive glycemia group, class 2 had a lower CAN risk (HR: 0.83, 95% CI: 0.72–0.96, $P = 0.014$), while class 3 had a higher risk (HR: 1.35, 95% CI: 1.05–1.73, $P = 0.018$), indicating that intensive therapy might affect the TyG index-CAN risk relationship.

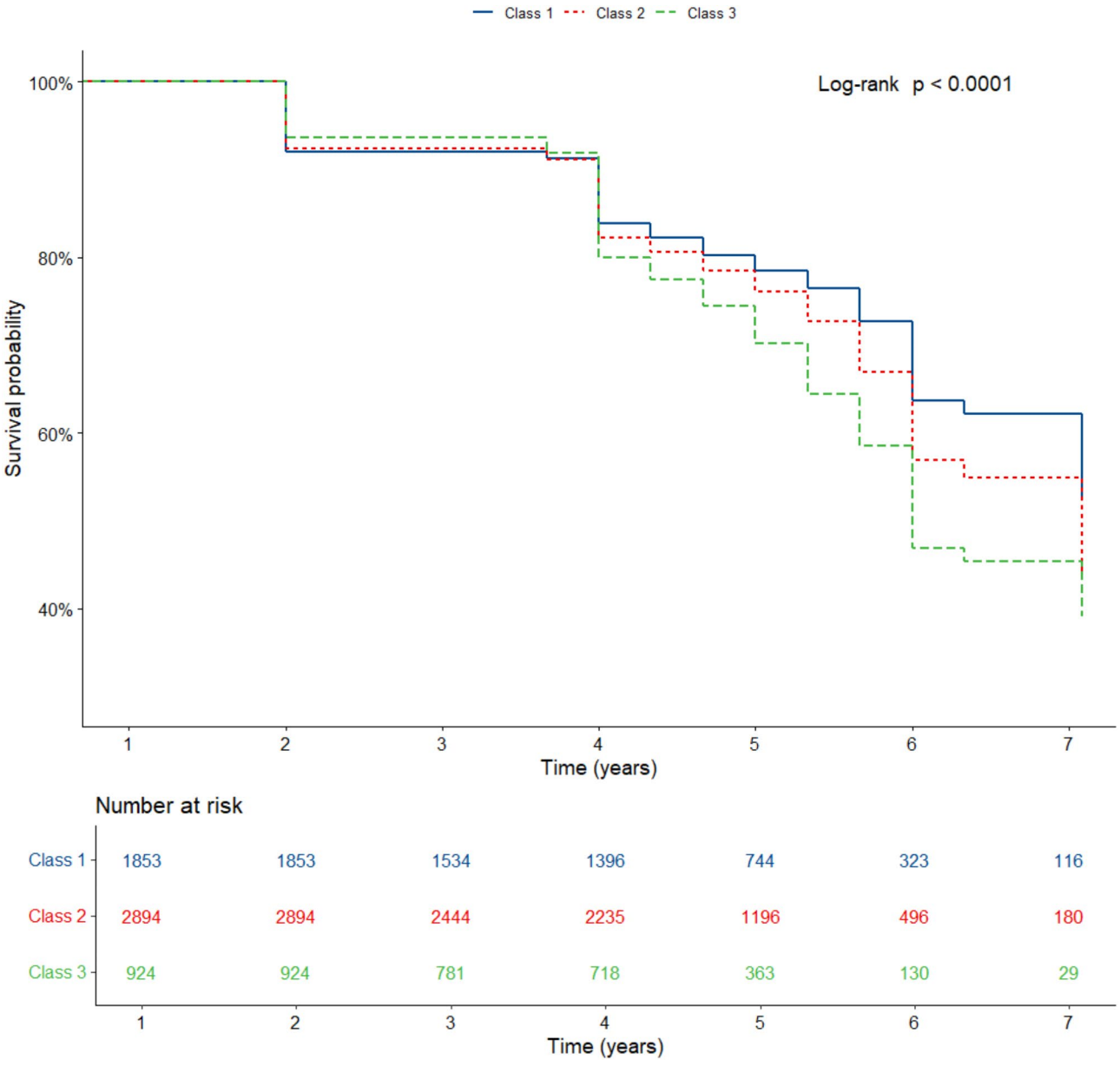


**Fig. 4** Kaplan-Meier survival curve for CAN incidence based on trajectory of TyG index. CAN, cardiovascular autonomic neuropathy; TyG, triglyceride-glucose

**Table 3** Association of trajectory of TyG index with CAN incidence

| | Crude Model | | Model I | | Model II | |
|---|---|---|---|---|---|---|
| | **Crude HR (95%CI)** | ***P*-value** | **Adjusted HR (95%CI)** | ***P*-value** | **Adjusted HR (95%CI)** | ***P*-value** |
| Class 1 | Reference | | Reference | | Reference | |
| Class 2 | 1.18 (1.05, 1.33) | 0.006 | 1.13 (1.01, 1.28) | 0.039 | 1.18 (1.03, 1.34) | 0.015 |
| Class 3 | 1.45 (1.25, 1.68) | < 0.001 | 1.37 (1.17, 1.60) | < 0.001 | 1.52 (1.26, 1.83) | < 0.001 |
| *P* for trend | < 0.001 | | < 0.001 | | < 0.001 | |

The crude model did not adjust for any covariates. Model I adjusted for age, gender, ethnicity and BMI. Model II adjusted for all covariates. TyG, triglyceride-glucose; CAN, cardiovascular autonomic neuropathy; HR, hazard ratio; CI, confidence interval; BMI, body mass index

## Discussion

CAN, a common T2D complication, is linked to higher cardiovascular disease mortality [32]. TyG index is a robust marker of insulin resistance, which is related to the increased risk of cardiometabolic diseases [9]. However, there is still lack of evidence between TyG index and CAN risk. In cross-sectional settings, we observed a positive link between baseline TyG index and CAN incidence

in T2D patients. Moreover, the TyG index had a good predictive performance according to the results of AUC after adjustment for potential confounders. Over a 7-year follow-up, we identified that three distinct TyG index trajectories using LGCM, showed a significant association with CAN incidence, which was consistent across different subgroups. Finally, our study found that intensive glycemic therapy might modify the relationship between trajectory of TyG index and CAN incidence. These findings indicate that elevated baseline and trajectory of TyG index contribute to the development of CAN.

Recent studies have proved that CAN is associated with gender, blood glucose levels, kidney function, and cardio-metabolic traits [33–35]. However, even after controlling for these factors, CAN is still associated with a higher mortality. The latest research indicates that insulin resistance is involved in the onset of CAN, especially in T2D [5]. Recently, TyG index has been emerging as a straightforward and dependable surrogate marker for insulin resistance [17, 36, 37]. Numerous investigations have scrutinized the correlation of TyG index with cardiovascular diseases across diverse cohorts [6, 38, 39]. Huang et al. demonstrated that an increased TyG index in hypertensive patients was linked to an elevated risk of stroke [8]. Similarly, Yan et al. identified that increased baseline TyG levels independently correlated with greater arterial stiffness [9]. Our study revealed that individuals with CAN had higher TyG index levels compared to those without CAN in T2D. Moreover, TyG index levels were positively associated with the incidence of CAN and demonstrated a good predictive value for CAN risk. Therefore, a relatively high baseline TyG index might serve as a risk factor for the development of CAN and could be a valuable indicator for CAN risk in patients with T2D.

Trajectory of TyG index refer to the patterns of change in the TyG index over time [26]. Trajectory captures the dynamic fluctuation and trend in TyG index, providing a more robust and reliable analysis of its long-term impact on the incidence of CAN. Trajectory of TyG index is frequently utilized to investigate the development of chronic diseases [39–41]. Tai et al. found that TyG index trajectory was linked to the occurrence of major adverse cardiovascular events in T2D patients [38]. Yu et al. highlighted that analyzing long-term TyG index trajectory could identify individuals at elevated risk for carotid atherosclerosis progression, guiding targeted prevention and treatment strategies [6]. This study tracked TyG index changes over 7 years in T2D patients and found that class 3 had a higher CAN incidence, with significant association between TyG trajectories and CAN risk confirmed in sensitivity and subgroup analyses. These studies have provided evidence that long-term TyG index trajectory is valuable in clinical practice for patients with T2D.

Blood glucose control is an essential element in diabetes management, aimed at preventing diabetes-related complications such as cardiovascular and renal diseases [42]. In the ACCORD study, intensive glycemia control aimed to achieve a target HbA1c level of <6% through more aggressive management of blood glucose, as compared to standard therapy, which targeted HbA1c levels of 7-7.9% [43]. However, recent randomized controlled trials on intensive glycemia treatment have yielded inconsistent and inconclusive results. Wang et al. found that intensive glycemia treatment lowered microvascular outcomes in individuals with low HbA1c variability, but increased risk in those with high variability [44]. Similarly, Huang et al. showed that intensive treatment improved cardiovascular outcomes in patients with low HRV but not in those with normal HRV [45]. In our study, intensive glycemic therapy had no significant impacts on CAN risk in class 1. However, it reduced CAN risk in class 2, possibly due to improved metabolic stability and fewer adverse events in this group [46]. Conversely, in class 3, intensive glycemic therapy significantly increased the risk of CAN. This finding aligns with previous studies showing that intensive therapy may result in higher rates of adverse events, including severe hypoglycemia and medication errors, particularly in patients requiring complex therapeutic regimens [47]. These results highlight the importance of tailoring intensive glycemic therapy to specific clinical subgroups, as it may benefit patients in class 2 but increase risks in class 3. Our findings emphasize the need for personalized glycemic targets in diabetes management. Intensive glycemic therapy should not be routinely applied to all patients but selectively tailored to decrease the risk of CAN in appropriate populations.

This research has several strengths, such as employing LCTM to examine changes in the longitudinal TyG index and performing sensitivity analyses to validate the results. Nevertheless, some limitations must be acknowledged. Because the study is observational, it is not possible to establish causal relationships definitively. Furthermore, despite conducting multivariate adjustments and subgroup analyses, the possibility of residual confounding persists. Finally, the predictive ability of TyG index, in combination with multiple variables for CAN, needs to be confirmed by further large sample studies.

## Conclusion

In conclusion, higher baseline and its trajectory of TyG index are associated with an increased incidence of CAN. Moreover, intensive glycemia treatment might modify the link between TyG index trajectory and CAN risk.

**Abbreviations**

| | |
|---|---|
| CAN | Cardiovascular autonomic neuropathy |
| TyG index | Triglyceride-glucose index |
| ACCORD | Action to Control Cardiovascular Risk in Diabetes |

| | |
|---|---|
| HRV | Heart rate variability |
| CVD | Cardiovascular disease |
| T2D | Type 2 diabetes |
| TG | Triglyceride |
| FBG | Fasting blood glucose |
| SDNN | Standard deviation of all normal-to-normal R-R intervals |
| rMSSD | Root mean square of successive differences between these intervals |
| BMI | Body mass index |
| RCS | Restricted cubic spline |
| LGCM | Latent growth curve model |
| BIC | Bayesian Information Criterion |
| HbA1c | Glycated hemoglobin |
| LDL | Low density lipoprotein |
| HDL | High-density lipoprotein |
| eGFR | Estimated glomerular filtration rate |
| SBP | Systolic blood pressure |
| DBP | Diastolic blood pressure |
| ALT | Alanine transaminase |
| CVD | Cardiovascular disease |
| ACEI/ARB | Angiotension converting enzyme inhibitors/angiotensin II receptor blockage |
| CCB | Calcium channel blockers |
| OR | Odd ratio |
| CI | Confidence interval |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02622-x .

Supplementary Material 1

Supplementary Material 2

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Not applicable.

**Author contributions**
Writing manuscript: QH; Data extraction and Statistical analysis: WBN; Project administration: BMH; Conceptualization and supervision: ZHX; Reviewing and editing: ZYP. All authors read and approved the final manuscript.

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**Data availability**
The datasets used and analyzed during the current study are available from the ACCORD/ACCORDION Research Materials obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center, https://biolincc.nhlbi.nih.gov/studies/accord/.

## Declarations

**Ethics approval and consent to participate**
Participants wrote informed consent for their involvement in the ACCORD study (ClinicalTrials.gov number, NCT00000620).

**Consent for publication**
All authors listed above approved the manuscript for publication.

**Competing interests**
The authors declare no competing interests.

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